

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

6

REMARKS/ARGUMENTS

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of two months of the period for response to the Office Action.

The consideration of the information disclosure statement filed October 28, 2004 and the withdrawal of the obviousness type double patent rejection are gratefully acknowledged.

The Examiner maintained the following rejections:

- rejection of claims 29, 35 and 37 to 40 under 35 USC 102(e) as being anticipated by Gurtiss III (US Patent No. 5,389,368)
- rejection of claims 30 to 32, 34 and 36 under 35 USC 103(a) as being unpatentable over Gurtiss III applied to claims 29, 35 and 37 to 40 in view of Brunham (WO 98/02546).

Reconsideration of these rejections is requested having regard to the submissions made herein and the amendments to claim 29.

Claim 29 is directed to a method of immunizing a host by administering to the host an attenuated bacteria harbouring a vector comprising a nucleic acid molecule encoding at least an immunoprotection-inducing *Chlamydia* protein or a fragment thereof which generates a *Chlamydia* protein specific immune response and a promoter actively coupled to the nucleic acid molecule for expression of the *Chlamydia* protein or fragment thereof in cells of the host but not in the attenuated bacteria. Claims 35 and 37 to 40 are dependent, directly or indirectly, on claim 29.

The key feature of claim 29 which serves to distinguish it from the Gurtiss III reference is that the *Chlamydia* protein is expressed in the host but not in the attenuated bacteria. As described in the specification, for example, on page 8, lines 7 to 15, the expression of the DNA is effected when the bacterial vector has released the DNA into the appropriate host cells, such as macrophage or dendritic

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

7

cells. After uptake of the bacterial vector by the cells, the anoxotrophic bacteria dies and the plasmid DNA then is released into the cytoplasm of the infected host cells and the encoded gene expressed in the host cells. Having regard to the Examiner's comments and analysis of the cited prior art, the distinctions over the prior art have been further clarified by amending claim 29 to recite that the *Chlamydia* protein or fragment is expressed by the cells of the host but not by the attenuated bacteria.

Gurtiss III provides a vaccine for immunization of a vertebrate or invertebrate comprising an avirulent derivative of a microbe. The derivative is substantially incapable of producing functional adenylate cyclase and cyclic AMP receptor protein while being capable of expressing a recombinant gene derived from a pathogen of the vertebrate or invertebrate to produce an antigen capable of inducing an immune response in the vertebrate or invertebrate against the pathogen (col. 3, ll. 42 to 50). Gurtiss III also disclose a method of stimulating the immune system of a vertebrate or invertebrate by administering the vaccine to the vertebrate or invertebrate (col. 3, line 60 to col. line 2).

Gurtiss III also describes a carrier microbe for the synthesis of a vertebrate or invertebrate host protein comprising the avirulent derivative of a pathogenic microbe which is capable of expressing a recombinant gene derived from a vertebrate or invertebrate host to produce a product capable of suppressing, modulating or augmenting an immune response to the vertebrate or invertebrate (col. 4, ll. 3 to 12).

It is clear from these passages that, in Gurtiss III, the avirulent microbe directs expression of the foreign antigen in the avirulent microbe. There is no disclosure in Gurtiss III of an avirulent microbe in which the foreign antigen is expressed by the host and not by the microbe, as required by applicants claims.

Thus, there is a fundamental difference between the attenuated bacteria defined in applicants claims and utilized in the method of immunization defined therein and the cited prior art. In the present invention, the attenuated

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

8

bacteria is employed as a carrier for the vector and it is the promoter in the DNA construct which directs expression of the *Chlamydia* protein or fragment thereof by the host cells only and not by the attenuated bacteria, quite the reverse of Gurtiss III.

In the Final Action, the Examiner states:

"it is the position of the Examiner that Gurtiss III.... discloses *Salmonella typhimurium*, *S. typhi* and other *Salmonella* species to evidence the ability to attach to, invade and proliferate in the cells of the gut-associated lymphoid tissue (GALT; Peyer's Patches) Thus, the *Chlamydia* protein (Gurtiss III, claim 6) is expressed in the eukaryotic host cell, as *Salmonella* is an intracellular pathogen."
(Examiner's emphasis)

It is submitted that the conclusion drawn by the Examiner is not supported by the disclosure of Gurtiss III.

It is agreed with the Examiner that the avirulent microbes preferably are derived from *Salmonella* (col. 6, ll. 12 to 15) and that *Chlamydia* is identified as a pathogenic microorganism useful in Gurtiss III constructs (claim 6 and also in col. 6, ll. 52 to 53). However, Gurtiss III states, in col. 6, ll. 16 to 34:

"In another embodiment of the invention, the avirulent derivative of a pathogenic microbe also referred to herein as a carrier bacteria can be used to deliver selected antigens to the GALT If these carrier bacteria contain and express a recombinant gene from a pathogenic organism, antibodies against the antigenic gene product produced from the pathogen will be induced. With the advent of recombinant DNA techniques, it now becomes possible to develop totally unique vaccines in which specific antigens are produced, not by the etiologic agent, but by another host strain of bacteria capable of expressing the gene for that antigen." (Emphasis added).

It is an absolutely clear from this passage that Gurtiss III is contemplating expression of the foreign gene by the avirulent bacteria. In addition, Gurtiss III defines the term "expression of a gene" as:

"Expression of a gene means that the information inherent in the structure of the gene is transformed into a physical product ... by the

Application No. 10/899,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

9

biochemical mechanisms of the cell. in which the gene is located."
(Emphasis added) (col. 9, ll. 37 to 43)

The patentee elaborates on the use of the avirulent microbe as a carrier (in col. 10, ll. 10 to 24):

".....once the carrier microbe is present in the animal, the antigen needs to become available to the animal's immune system. This may be accomplished when the carrier microbe dies so that the antigen molecules are released. ... In this way, it is possible to use a viable microbe that will, persist in the vaccinated animal, for example, in the Peyer's patches and continue to produce antigen, thereby continually inducing antibody formation." (Emphasis added)

It is clear, therefore, that Gurtiss III contemplates only expression of antigen by the carrier avirulent microbe. The reference contemplates no production of antigen following death of the carrier microbe. Any antigen is produced only by the avirulent microbe, even after uptake by the Peyer's patches.

The Examiner asserts in the Final Action that:

"Inherently the reference anticipates the instantly claimed invention because Salmonella-mediated delivery of a nucleic acid molecule encoding a Chlamydia antigen to the GALT elicits an immune response because the avirulent Salmonella mutants have lost the ability to cause disease without impairment in their ability to attach to and invade the GALT, and the instantly claimed invention has not been distinguished from the Invention of Gurtiss III."

It is submitted, for the reasons discussed above with reference to disclosure of Gurtiss III, that the reference does not "inherently anticipate" the claimed invention. It is agreed that the avirulent Salmonella molecule have lost their ability to cause disease without impairment of their ability to invade the host. As discussed above, Gurtiss III, discloses that, following invasion of the Peyer's patches, the avirulent Salmonella releases the antigen it produces to the Peyer's Patches. There is no suggestion in Gurtiss III that the Peyer's patches themselves are producing antigen. It is only the Salmonella which produces antigen. As to distinction of the claimed

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

10

invention over Gurtiss III, it is submitted that applicants claim language clearly distinguishes over the disclosure of Gurtiss III as discussed above:

"An attenuated bacteria harbouring a vector comprising a nucleic acid molecule ... and a promoter operatively coupled to said nucleic acid molecule for expression of said *Chlamydia* protein or fragment thereof by cells of the host but not by said attenuated bacteria." (Emphasis added)

In Gurtiss III, the antigen is always produced by the attenuated bacteria.

As pointed out in response to the prior Office Action, the earliest date of filing of Gurtiss III (June 1987) predates any notion of DNA immunization to effect foreign gene expression by a host to which an expression vector is administered. It is believed that Ulmer et al (1993, ref. 39 herein) is the earliest paper contemplating DNA immunization.

In response to the prior Office Action, the applicants pointed to the discussion in the patent application with respect to the relevance of Gurtiss III and the apparent agreement of the Examiner thereto in allowing that application, which subsequently granted as US Patent No. 6,676,949. In the Final Action, the Examiner points to differences in the scope of the claims pending in this application and those of the granted US Patent, arguing that the traversal was not communicate in scope with the instantly claimed invention. While not specifically agreeing with the Examiner's position, the applicants are content not to pursue this argument further at the present time.

In response to the prior Office Action, the applicants had stated:

"It is the promoter in the DNA construct that directs expression of the MOMP in the host cells only and not in the attenuated bacteria."

The Examiner takes issue with this statement in the Final Action, stating that:

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

11

"It is the position of the Examiner that Gurtiss teaches attenuated *Salmonella* strains as carrier (see col. 8, line 49; col. 10, lines 10 to 12) for a vector (see col. 9, lines 29 to 35) that contains a nucleic acid that encodes a *Chlamydia trachomatis* antigen (Gurtiss, claim 6) and the expression of the encoded gene product is accomplished by a promoter operatively coupled to the nucleic acid in the expression vector (see col. 11, lines 39 to 45, col. 26, lines 6 to 22, Tables 1, col. 16, Table 10, col. 28). *Salmonella* are invasive bacteria and would express the vector upon the entry into the animal host cells. The attenuated *Salmonella* of Gurtiss would express the carried vector in the host cells."

While *Salmonella* are invasive bacteria, there is no contemplation whatsoever in Gurtiss that a vector harboured by the attenuated *Salmonella* would enter into the animal host cells and that the host cells would express a *Chlamydia* antigen or fragment thereof. In this regard, the Examiner attention is directed to the above quotation from Gurtiss, col. 10, ll. 10 to 24.

While the Examiner is correct that *Salmonella* are invasive bacteria and would express the vector upon entry into the animal host cell, it is clear from the disclosure of Gurtiss that it is the *Salmonella* strains which express the antigen to the invaded cells and not the cells themselves. Again, the Examiner's attention is drawn to col. 10, ll. 10 to 24. In fact, it would appear that the Examiner agrees, in reading the statement:

"The attenuated *Salmonella* of Gurtiss III would express the carried vector in the host cells." (emphasis added).

Applicants claim language specifically requires that the *Chlamydia* protein or fragment not be expressed in the bacteria.

Looking at the passages of Gurtiss III to which the Examiner refers, it is agreed with the Examiner that Gurtiss teaches attenuated *Salmonella* strains as carriers. However, the passages must be placed in context. In col. 8, line 49, it is indicated that the avirulent microbe is a carrier of the gene product. Col. 10, ll. 10 to 12 has been discussed above. The passage just says that the antigen, which is

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

12

produced by the attenuated *Salmonella*, needs to become available to the immune system.

Col. 9, lines 29 to 35 is part of a long passage (col. 8, line 64 to col. 9, line 63) describing techniques for transferring genetic material from a first organism to a second organism which normally does not exchange genetic material with the first organism by recombinant DNA technology and defines a gene.

Col. 11, lines 39 to 45 is part of a longer passage describing recombinant DNA techniques (col. 11, ll. 17 to 47), and describes transformation of organisms. Col. 26, lines 6 to 22 is part of a passage describing with the construction and testing of bivalent vaccine strain to immunize against *Bordetella avium*. It is quite clear from the quoted passage that *B. avium* proteins are produced by the *Salmonella* and are released to stimulate an immune response when the vaccine strain colonizes the Peyer's patches. The recombinant clones are tested to ensure expression of the genes in the *Salmonella*. (col. 26, ll. 17 to 22).

Table 1 in col. 16 and Table 10 in col. 20 are simply Tables of bacterial strains.

These particular passages to which the Examiner refers serve to reinforce applicant's position that Gurtiss III discloses only expression of the antigen by the *Salmonella* or other attenuated bacteria and there is no disclosure of entry of any vector into the host cells and expression therefrom, nor the means to do so.

With respect to the Examiner's comments on the arguments presented not being commensurate in scope with what is claimed in claims 29, 35, 37 to 40, the Examiner is correct that applicant's submissions should have been made with respect to the broader language of a *Chlamydial* protein or fragment thereof. The statement remains correct in the wider context of the language of claim 29.

The Examiner further states in the Final Action:

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

13

"Two types of host cells are recited in the claims, bacterial host cell and host cells. Salmonella is a host cell that replicates in animal host cells, which results in the induction of the vector encoded nucleic acid molecule expression in the host cells. Applicants arguments are not commensurate in scope with the claimed invention."

In this regard, it is submitted that the amendment to the claim language of claim 29 as discussed above clarifies the matter and applicants arguments are commensurate in scope with the language of the claims.

In any event, it is clear from the above discussion of the disclosure of Gurtiss III that when the Salmonella is taken up by "host cells", by Peyer's patches, the expression of the vector "in" the host cells is antigen expression from the Salmonella. There is no contemplation in Gurtiss that antigen expression other than by the Salmonella, a condition excluded from applicants claims.

In addition, the Examiner states in the Final Action:

"The expression of the encoded nucleic acid molecule would be in animal host cells that have been invaded by the attenuated bacteria. Salmonella is an invasive bacterial, the attenuated strain of Gurtiss are taught to be invasive attenuated strain, and the vector would find expression in the host cells, upon the attenuated Salmonella invading the cell."

Again, applicants have amended the claim language of claim 29 to clarify that the expression of the *Chlamydia* protein or fragment is by cells of the host and not by the attenuated bacteria. In Gurtiss, the expression is by the attenuated bacteria and not by cells of the host.

In the Final Action, the Examiner states:

"....Gurtiss teaches the in vivo expression of a heterologous nucleic acid in an attenuated bacteria that is in host cells. The expression of the nucleic acid molecule takes place in host cells based upon the expression vector in the attenuated bacteria."

As discussed in detail above, it is correct that the expression of the nucleic acid molecule takes place in the attenuated bacteria. As also discussed above, the

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

14

language of claim 29 has been amended to clarify that the promoter is operatively coupled to the nucleic acid molecule of expression of the *Chlamydia* protein or fragment thereof by cells of the host not by the attenuated bacteria.

The Examiner goes on to state:

"Applicant has not claimed a method of DNA immunization of an immunocompetent animal, but claims a method of stimulating an immune response utilizing an attenuated bacteria that expresses a heterologous coding sequence for a protein. There is no requirement that the host cells to be transformed, but only the vector find expression in host cells."

It is submitted that it is inherent in the language now used that the host cells are transformed.

Having regard to the above discussion, it is submitted that claims 29, 35 and 37 to 40 are not anticipated by Gurtiss III and hence the rejection of claims 29, 35 and 37 to 40 under 35 USC 102(e) as anticipated by the prior art, should be withdrawn.

Turning now to claims 30 to 32, 34 and 36 under 35 USC 103(a) as being unpatentable over Gurtiss III, in view of Brunham, the Brunham reference is relied on for teaching specific *Chlamydia* nucleic acid molecule and a specific promoter "this is taught to be combinable to form a vaccine that contains antigenic material from more than one pathogen (see page 13, lines 19 to 24)."

Brunham describes a vector comprising a nucleic sequence encoding a MOMP or MOMP fragment and a promoter sequence operatively coupled to the mutated sequence for expression of the MOMP in a host and the production of an immune response to the MOMP upon administration of the vector to the host.

Page 13, lines 19 to 24, to which the Examiner refers, simply states that vaccines that contain antigenic materials from several pathogens are known as combined vaccines.

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

15

While, as the Examiner observes, Brunham teaches with incorporation of the plasmid vector into an attenuated *E. coli* bacterial strain, this is for the purpose of amplification of the amount of the plasmid by growing the *E. coli* and subsequently recovering the plasmid vector DNA.

The Examiner considered that:

"Gurtiss III provides motivation to combine the promoter/MOMP nucleic acid molecule/vector of Brunham with the Salmonella of Gurtiss III because the attenuated Salmonella serves to carry the encoded nucleic acid molecule in a host cell. for immunizing a host (see col. 34, ll. 32 to 39; col 35, line 8) and provides sight directed vector delivery system to host cells (see col. 8, ll. 47 to 51, col. 7, ll. 27 to 29)."

First of all, the vector described in Brunham is intended for DNA immunization where the host cells express the MOMP and results in an immune response to the MOMP. As has been extensively discussed above, the constructs described in Gurtiss are designed for expression of the antigen by the attenuated bacteria. Whether the attenuated bacteria invade host cells, the mechanism remains the same and the antigen is expressed by the attenuated bacteria and not by the host cells. Since the vectors are fundamentally different in mechanism of operation, it follows that there is no motivation to utilize the vector of Brunham in the attenuated bacteria of Gurtiss III.

Accordingly, it follows that claims 30 to 32, 34 and 36 are patentable over the applied combination of prior art and hence the rejection of such claims under 35 USC 103(a) as being unpatentable over Gurtiss III in view of Brunham, should be withdrawn.

The patent numbers for pending applications which have now proceeded to grant have been added to pages 4 and 9.

Entry of this Amendment after Final Action is requested in that the application thereby is placed in condition for allowance. In the event the Examiner considers that the Amendment does not place the application in condition for

Application No. 10/699,882
Amdt. dated August 22, 2005
Reply to Office Action of May 9, 2005

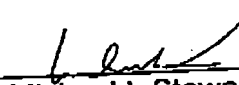
16

allowance, the Amendment nevertheless should be entered, since the claims thereby are placed in better form of appeal.

In the event the Examiner considers that further modification to the claim language is desirable to define the patentable subject matter thereof, the Examiner is requested to call. the undersigned, Mr. Michael Stewart, collect, at the number given below, in order to arrive at mutually-acceptable language.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,


Michael I. Stewart
Reg. No. 24,973

Toronto, Ontario, Canada,
(416) 595-1155
FAX No. (416) 595-1163